

**INTERVENTIONS TO CURB HEPATITIS C REINFECTIONS
AMONG MEN WHO HAVE SEX WITH MEN**

The ICECREAM study

A Randomized Trial

INTERVENTIONS TO CURB HEPATITIS C REINFECTIONS AMONG MEN WHO HAVE SEX WITH MEN

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| Project leader | <p><i>Marita van de Kerkhof, MSc, PhD Student, Public Health Service of Amsterdam, University of Amsterdam</i></p> <p><i>mvdkerkhof@ggd.amsterdam.nl</i></p> <p><i>020-5553711</i></p> |
| Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) | <p>Public Health Service of Amsterdam</p> <p><i>Prof. dr. Maria Prins, professor of Public Health and Epidemiology of Infectious Diseases at the Amsterdam University Medical Centers (UMC), Location Academic Medical Center (AMC), University of Amsterdam and head of the Department of Infectious Diseases Research and Prevention of the Public Health Service of Amsterdam</i></p> <p>Amsterdam UMC, Location AMC</p> <p><i>Dr. M. van der Valk, Infectious Diseases specialist and head of the HIV clinic, Amsterdam UMC location AMC</i></p> <p>DC Clinic Lairese, Amsterdam</p> <p><i>Dr. M. van der Valk, Infectious Diseases specialist and head of the HIV clinic, DC Clinic Lairese Amsterdam</i></p> <p>Medical Center Jan van Goyen</p> <p><i>Dr. D.W.M. Verhagen, Infectious Diseases specialist,</i></p> |

| | |
|---|---|
| | <p>Medical Center Jan van Goyen</p> <p><i>Onze Lieve Vrouwe Gasthuis</i></p> <p>Prof. dr. K. Brinkman, Infectious Diseases specialist, Onze Lieve Vrouwe Gasthuis</p> <p><i>VU Medical center</i></p> <p>Dr. E.J.G. Peters, Infectious Diseases specialist, VU Medical Center</p> |
| Sponsor (in Dutch: verrichter/opdrachtgever) | <i>Public Health Service of Amsterdam (GGD Amsterdam)</i> |
| Subsidising party | <i>The Netherlands Organisation for Health Research and Development (ZonMw)</i> |
| Independent expert | <i>Prof. dr. Joost Wiersinga, MD PhD, chair of the Division of Infectious Diseases, Amsterdam UMC, Location AMC, University of Amsterdam</i> |
| Laboratory sites | <i>Virology Laboratory at the Medical Microbiology department of the UMC location AMC Dr. Janke Schinkel</i> |
| Pharmacy | <i>Not applicable</i> |

PROTOCOL SIGNATURE SHEET

| Name | Signature | Date |
|--|------------------|-------------|
| Head of Department/Principal Investigator: <i>Prof. dr. Maria Prins, professor of Public Health and Epidemiology of Infectious Diseases at the AMC and head of the Department of Research and Prevention of the Public Health Service of Amsterdam</i> | | |

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|-----------------------|--|
| AMPrEP project | Amsterdam PrEP project |
| ANRS | The National Agency of Research on AIDS and viral hepatitis |
| CMS | Content Management System |
| DAA | Direct-Acting Antivirals |
| DBS | Dried Blot Spots |
| DSMB | Data Safety Monitoring Board |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| IMB model | Information-Motivation-Behavioural skills model |
| ICECREAM | Interventions to Curb hEpatitis C Reinfections Among Men who have sex with men |
| InPrEP project | Informal PrEP project |
| ITT | Intention To Treat |
| METC | Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC) |
| MOSAIC | MSM Observational Study of Acute Infection with hepatitis C |
| MSM | Men who have Sex with Men |
| NGO | Non-Governmental Organization |
| OR | Odds Ratio |
| PP | Per Protocol |
| PrEP | Pre-Exposure Prophylaxis |
| RNA | RiboNucleic Acid |
| ROC | Receiver Operating Characteristic |
| RT | Randomized Trial |
| SHM | The Dutch HIV monitoring foundation (in Dutch: Stichting HIV Monitoring) |
| STI | Sexually Transmitted Infection |
| SVR | Sustained Virological Response |
| WHO | World Health Organization |
| WMO | Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen) |
| ZonMw | The Netherlands Organisation for Health Research and Development (in Dutch: Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie) |

SUMMARY

Rationale: As highly effective therapy against hepatitis C virus (HCV) infection is available with rapid uptake, there is newfound optimism for HCV elimination. Nevertheless, HCV reinfections cause great concern in at risk populations, including men who have sex with men (MSM). In the Netherlands, MSM account for the majority of new HCV (re)infections. Although HCV treatment uptake is high in this group, modelling data indicate HCV elimination would not be feasible without a reduction in risk behaviour. This finding highlights the urgent need for effective interventions aimed at reducing risk behaviour and preventing reinfections in MSM.

Objective: To evaluate interventions aimed at reducing risk behaviour, and ultimately preventing HCV reinfections and onward spread of HCV.

Study design: Using a 3-arm randomised trial comparing run-in and intervention periods, we will evaluate the effect of two interventions and its combination on risk behaviour in MSM previously infected with HCV.

Study population: MSM aged 18 years or older with a history of a successfully treated or spontaneously cleared HCV infection.

Interventions: Intervention I is a targeted, online behavioural intervention developed as part of the project. Intervention II aims to increase the frequency of testing by offering an additional patient-initiated, home-based HCV RNA testing service with the use of self-sampled dried blot spots. Intervention III is a combination of intervention I and II.

Main study parameters/endpoints: From run-in and post-randomization questionnaires, we will evaluate the proportion at risk of HCV infection (as determined by the HCV-MOSAIC score) as the primary outcome. The HCV-MOSAIC risk score is calculated by summing up the beta coefficients specific to six self-reported risk factors when present: receptive condomless anal sex (beta 1.1), sharing sex toys (beta 1.2), unprotected fisting (beta 0.9), injecting drug use (beta 1.4), sharing straws during nasally-administered drug use (beta 1.0), and ulcerative sexually transmitted infection (beta 1.4). Secondary outcomes include incidence of HCV reinfection, changes in the individual risk behaviour items and changes in sexual wellbeing.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: One site visit will be required for all participants to sign the informed consent form. All further study procedures will be web-based or will take place from home. Participants will be exposed to five online questionnaires, with an interval of 6 months. The questionnaires and interventions can make participants more aware of their HCV risk, which could make participants feel at unease. However, we think this study poses negligible risk to the participants.

1. INTRODUCTION AND RATIONALE

1.1 Background

Hepatitis C Virus (HCV) infection may lead to liver inflammation, cirrhosis, liver cancer and death. HCV is a global health problem; about 71 million individuals worldwide are infected and every year, 495,000 deaths from HCV infection occur and the burden of disease continues to rise.¹⁻³ HCV is usually spread through blood-to-blood contact. Since 2000, outbreaks of sexually transmitted HCV infection have been reported among HIV-positive men who have sex with men (MSM). Risk factors independently associated with the acquisition of acute HCV among MSM include sexual risk behaviour (e.g. unprotected anal intercourse, unprotected fisting) and recreational drug use.⁴ HIV/HCV coinfection results in an increased risk of both HCV and HIV related mortality.^{5, 6} Currently, there is no vaccine available to prevent HCV infection. A small proportion (10-15%) of HIV-positive MSM will spontaneously clear the infection without treatment.^{7, 8} Recent availability of highly effective oral HCV therapy (direct acting antivirals (DAA)) for HCV infection with cure rates of 95% has created optimism towards HCV elimination.

1.2 HCV in the Netherlands

The Dutch HCV epidemiological patterns are quite unique and the country seems to be in a good position for reaching elimination goals. The Netherlands is a country with one of the lowest HCV prevalence in the general population worldwide³ with rapid uptake of interferon-free treatment since unrestricted access (i.e., no longer fibrosis stage restrictions) to DAA for all chronic HCV patients was authorized in November 2015. Hence, reaching the World Health Organization (WHO) HCV elimination goals (i.e., 90% reduction in new chronic infections, 65% reduction in mortality)⁹, might be more feasible in the Netherlands than in other regions. Importantly, in contrast to other regions, over the last decade we have observed almost no acute HCV initial and reinfections among the classical HCV risk group of people who inject drugs, related to a high uptake of comprehensive harm reduction programs.¹⁰⁻¹³ Thus, MSM are the sole group with ongoing HCV spread.

1.3 HCV among men who have sex with men

New HCV infections are typically found in HIV-positive MSM. Incidence of initial infection among HIV-positive MSM stabilized and was not markedly declining before DAA became widely available.¹⁴⁻¹⁶ Since unrestricted DAA availability in November 2015, HCV incidence has been decreasing in the Netherlands.^{17, 18} The incidence rate of acute HCV infection among HIV coinfecting MSM in HIV care was 4.5 diagnoses per 1,000 PY in 2012, 6.6 in

2015 and 3.3 in 2017.¹⁸ International data show diverging trends. In Switzerland and France for example, HCV incidence in MSM has remained stable or has shown an increase respectively^{19, 20}, since the availability of DAA's.

Of great concern is the more than ten times higher risk of reinfection when compared to initial infection; approximately one third of the MSM who successfully responded to HCV treatment acquired a reinfection within 2 years.^{21, 22} A subsequent high incidence of HCV reinfection has also been observed in other high income countries in MSM who both respond to treatment or clear the infection spontaneously.^{23, 24} An additional concern is the recent finding of a higher HCV prevalence (4.8%) in high risk HIV-negative MSM than previously reported.²⁵ These HCV mono-infected MSM applied for pre-exposure prophylaxis (PrEP) to prevent HIV infection and were infected with HCV strains already circulating among HIV-positive MSM. More recent data shows that the HCV incidence rate in HIV negative MSM on PrEP comparable is to that of HIV-positive MSM.^{20, 26} Increasingly overlapping sexual networks between HIV-positive and HIV negative MSM^{27, 28} might put these HIV-negative MSM also at risk of HCV reinfection and spread to the larger population of HIV-negative MSM cannot be excluded.

1.4 HCV treatment

The rapid uptake of DAA might contribute to HCV elimination. In the favourable Dutch epidemiological setting, targeting HIV/HCV coinfecting patients, of whom 69% are MSM²⁹, is a logical first step towards elimination as an estimated 90% of all HIV-positive persons living in the Netherlands are regularly seen in HIV care.¹⁸ It is promising that 15 months after broadening access of DAA therapy to all HIV/HCV-coinfecting patients independent of fibrosis stage, 82% of 1471 HIV/HCV coinfecting patients in the Netherlands had either achieved a sustained virological response (SVR12) or were currently still on DAA therapy.^{29, 30} Treatment uptake and cure rates were highest in MSM.²⁹ However, modelling data indicate that even in a setting with high DAA uptake among MSM, HCV elimination would not be feasible without a reduction in risk behaviour.^{31, 32} This reduction could be difficult to achieve as it might be that the new highly effective and well-tolerated treatments result in a decreased perceived threat of HCV, especially in those successfully treated with DAA and at risk of HCV reinfection. An increase in risk behaviour could likely surface and counteract treatment benefits.³³ Data indicate that MSM successfully treated with DAA are still at substantial risk of HCV reinfection.³⁴ This and the costs related to treatment of (re)infections highlight the urgent need for effective interventions aimed at reducing risk behaviour and preventing reinfections among MSM.

1.5 Interventions to prevent HCV reinfection

Effective interventions to prevent HCV reinfection targeting MSM are lacking. To our knowledge, behavioural interventions aimed at reducing risk behaviour for HCV transmission in MSM have only been studied within the Swiss HCVfree trial.³⁵ Preliminary results indicated that adding a behavioural intervention to HCV treatment was feasible³⁶, however the results on behavioural outcomes have not been published yet. The behavioural intervention reported by the Swiss was offered to HIV/HCV co-infected MSM with inconsistent condom use and occasional sex partners, and accompanied the treatment phase of the study.³⁷ Participants received four 45-minutes individual sexual risk counselling sessions, assisted by an interactive online tool (n=51). This intervention was an adaptation of a previous European randomized multi-center study targeting safer sex in HIV-positive MSM³⁸ In this randomized controlled trial, the intervention showed short-term effectiveness in HIV-positive MSM; condom use at last intercourse increased more among intervention than control participants at 3 months follow-up (odds ratio of 3.83; 95% confidence interval 1.15 to 12.76, $P = 0.03$), but not significantly at 6 months follow-up. In addition to behavioural interventions focusing on inconsistent condom use (such as the Swiss HCVfree trial), effective behavioural interventions targeting the wider range of HCV-related risk behaviours are urgently required for MSM at risk for HCV reinfection.

Additionally, more frequent testing for HCV might have the potential to change behaviour. Infection status notification can lead to a reduction in risk behaviour, as has been demonstrated for positive HIV and HCV test results.³⁹⁻⁴² There has been relatively little evidence about the effect of receiving a negative test result. Studies evaluating the effect of testing HIV-negative in MSM have found heterogeneity in how individuals respond to a negative test.^{43, 44} There is some evidence that (repeated) negative testing may increase sexual risk behaviour.^{43, 45-47} On the other hand, more frequent testing could lead to earlier detection of HCV reinfection and early treatment. Early treatment reduces the duration that reinfected patients may transmit HCV to their sex partners, hereby preventing new HCV infections on a population level.³² Notably, home-based testing using dried blot spots (DBS) offers advantages for HCV testing, as it has shown to increase convenience, anonymity, perceived control over the testing procedure, patient autonomy and control over the own health.⁴⁸

This project will set up, offer and evaluate two interventions (i.e. an online behavioural intervention and a home-based HCV testing intervention), alone or in combination, and possibly contribute to halting HCV transmission to the wider community of HIV-positive and HIV-negative MSM.

2. OBJECTIVES

Primary Objective:

To investigate whether the online behavioural and testing intervention, alone or in combination, causes a reduction in at risk behaviour compared to the run-in period (see [Chapter 7.1.1](#))

Secondary Objective:

To evaluate the impact of the behavioural and testing intervention, alone or in combination, on reinfection incidence, STI incidence, individual HCV related risk behaviour items and sexual wellbeing. Furthermore, we will evaluate the impact of the interventions on reinfection incidence and onward transmission using mathematical modelling.

3. STUDY DESIGN

We will perform a multi-center 3-arm randomized trial (RT) evaluating the effect of an online behavioural intervention, a home-based testing intervention, or a combination of both on HCV risk behaviour (**Figure 1**). The trial will start with a 6 month run-in period (standard care). This 6 month run-in period is used to determine at-risk behaviour under no intervention. Including a control comparator arm with no intervention was deemed unappealing to MSM (personal communication, Paul Zantkuijl, Soa Aids Nederland (NGO)) and could lead to high attrition rates. Hence, we decided that the risk of non-differential loss to follow-up would outweigh any benefit with using a control arm and we opted for a run-in comparison period instead. The intervention period will start at month 6 of the study period. Participants will be randomly assigned to one of the three arms (1:1:1 randomization). During this period, participants will receive standard care plus one or both interventions. Follow-up in the intervention period will end after 18 months. In total, five questionnaire measuring risk behaviour over the past period will be offered online every 6 months in the run-in period and intervention period (i.e., at month 0, 6, 12, 18 and 24 of the study period). This study will be viewed as a pilot approach to evaluate, within each arm, if a significant decrease in at-risk behaviour can be observed during the intervention period.

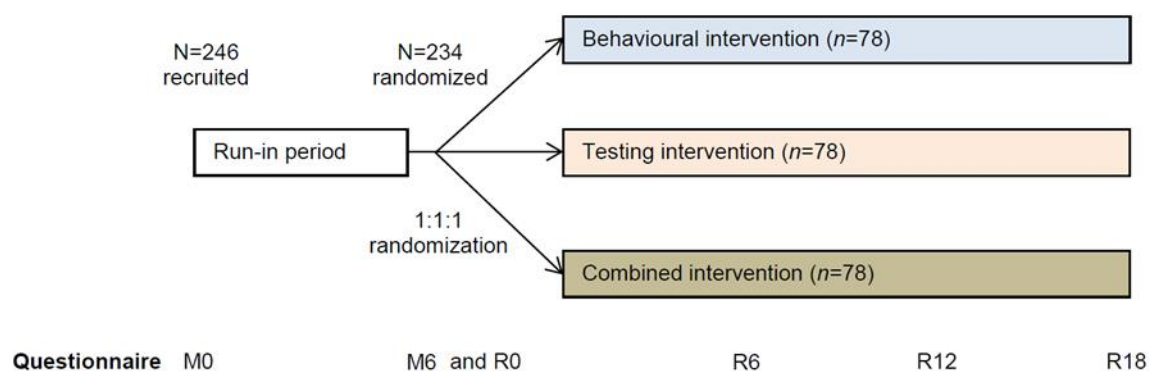


Figure 1: Study design of the ICECREAM study

4. STUDY POPULATION

4.1 Population (base)

The target population consists of MSM previously infected with HCV and currently in care at an HIV treatment center or visiting an STI/PrEP/sexual health center.

HIV-positive MSM with a history of HCV infection

In 2017, 1022 HIV/HCV coinfecting MSM retained in HIV care in the Netherlands, of whom 910 underwent HCV treatment.²⁹ We will recruit participants at five HIV treatment centers in Amsterdam:

- Onze Lieve Vrouwe Gasthuis, 200 HIV-positive MSM with a history of HCV infection retain in HIV-care.
- Amsterdam UMC - location AMC, 150-200 HIV-positive MSM with a history of HCV infection retain in HIV-care.
- DC Clinic Lairese, 75-100 HIV-positive MSM with a history of HCV infection retain in HIV-care.
- Medical Center Jan van Goyen, 30 HIV-positive MSM with a history of HCV infection retain in HIV-care.
- VU Medical Center, 30 HIV-positive MSM with a history of HCV infection retain in HIV-care

HIV-negative MSM with a history of HCV infection

HIV-negative MSM with a history of a HCV infection will be invited to participate during their visits for STI or PrEP related care. We will start recruitment at two STI/PrEP centers:

- Public Health Service of Amsterdam (GGD Amsterdam):
 - STI outpatient clinic: < 10 HIV-negative MSM were found to have a current or past HCV infection.
 - PrEP demonstration projects: there are three PrEP projects currently ongoing in HIV-negative MSM: (1) the Amsterdam PrEP (AMPreP) project, (2) the Informal PrEP (InPreP) project and (3) the DISCOVER study. All PrEP projects will end in 2020. In total, 31 MSM were found to have a current or past HCV infection at baseline or during follow-up.
 - Amsterdam Cohort Studies: in total < 5 HIV-negative MSM were found to have a current or past HCV infection at baseline or during follow-up.
- DC Clinic Lairese: < 10 HIV-negative MSM with a history of a HCV infection receive PrEP care at the DC Clinic Lairese.

In the Netherlands, the incidence rate of HCV is high among MSM who (start) using PrEP and comparable to that observed among HIV-positive MSM.^{25, 26} The Minister of Health announced that PrEP will partially be reimbursed and PrEP related care will become available by mid 2019 for 5 years for key groups who are at risk for HIV acquisition (estimated 8,500 MSM).^{49, 50} It is unclear how the scale-up of PrEP will affect HCV incidence and prevalence among HIV-negative MSM in the coming years. As PrEP use increases, condomless anal sex is likely to continue to rise⁵¹, as well as overlap between sexual networks of HIV-positive and HIV-negative MSM.²⁵ Both might lead to the spread of HCV to the larger population of HIV-negative MSM.

A potential risk is the willingness of MSM to participate in the randomized trial evaluating the effectiveness of interventions. We will strive to maximize the number of recruitment sites in the Netherlands. Also international collaborators showed their interest in the randomized trial. We submitted a grant application to the Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS) in France in March 2019 to extend the trial to three clinical centres in Paris. The grant was awarded by the ANRS in July 2019. Preparations for the project in France will start in January 2020.. The multidisciplinary approach and the involvement of all stakeholders including NGOs and end users from the beginning of the project onwards will optimize communication strategies and will match the needs of the target population of MSM, enhancing their participation. Furthermore, we would like to emphasize the “pilot” nature of the RT.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Informed consent documented by signature.
- Male individual aged 18 years or older.
- History of a cured or spontaneously cleared HCV infection (positive HCV RNA test in the past and/or positive anti-HCV IgG).
- Self-reported MSM who are either (i) HIV-positive seeking care at an HIV treatment center or (ii) HIV-negative and seeking care at an STI/PrEP/sexual health center.
- Sufficient understanding of Dutch or English.
- Have internet access and an e-mail address.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Acute or chronic HCV infection at time of enrolment.
- Under HCV treatment at time of enrolment.
- Unlikely, in the opinion of the clinician, to comply with the study procedures.
- Currently participating in an intervention study that offers extra HCV testing and/or a behavioural intervention targeting risk behaviour.
- Investigators or otherwise dependent persons.

4.4 Sample size calculation

We aim to have a minimum of 78 MSM per arm (total: 234). Assuming a drop-out rate of a maximum 5% in the run-in period (based on our experience with ongoing studies), we aim to enrol 246 MSM in total (see [Figure 1](#)). As we have no initial data on the effects of our interventions, we simulated power under varying conditions of at risk behaviour during the run-in period and absolute risk reduction during the intervention. With a sample size of 78 in each arm, we would have 80% power to demonstrate a statistically significant difference, at a type 1 error of 0.05, of a >22% reduction in the primary end-point from a 60% baseline prevalence of MSM identified as at risk (HCV-MOSAIC score ≥ 2.0 , see [Chapter 9.1](#)). When testing for differences in reduction of the primary end-point between two intervention arms ([Chapter 9.1](#)), while additionally assuming a 10% reduction in the comparator arm, we would have 80% power to demonstrate a statistically significant difference if a reduction of 0.43 was observed in the other intervention arm.

5. TREATMENT OF SUBJECTS

Both interventions will be offered online after randomization at month 6. The participants will be referred to the assigned interventions on the (ICECREAM) study website.

5.1 Arm I: behavioural intervention

The first arm consists of a web-based behavioural intervention. The behavioural intervention will be based on the principles of the Information-Motivation-Behavioural Skills (IMB) model for behavioural change, which was found effective in the context of HIV prevention and treatment adherence.^{52, 53} When adapted to the context of HCV, the IMB model assumes that acquisition of or improvement in HCV prevention related knowledge and motivation will increase the likelihood of the practice of risk-reduction behaviour either directly or in combination with the improvement of related behavioural skills. In our study we assume that the acquisition of new skills will be decisive for the success of our behavioural intervention. The online tailored intervention that is currently being developed will address barriers to and skills of applying risk reduction strategies. The intervention will consist of several modules to counteract the barriers for reducing sexual risk behaviour identified in our previous qualitative study³³, which include the following: (1) lack of knowledge regarding effective risk reduction strategies for HCV reinfection, (2) risky behavioural norms, and (3) existing behavioural patterns in the sexual network that are difficult to manage or change and result in social pressure towards risk. Furthermore, the intervention will address HCV-related stigma and non-disclosure of HCV status and drug use, as the latter is strongly present in the context of sex clubs and (group) sex and directly influence the self-efficacy of men to implement risk reduction measures.⁵⁴

The structure of the behavioural intervention will partially be based on the e-health assisted counselling intervention embedded in the Swiss HCVree trial (mentioned in [Chapter 1.4](#)). The behavioural outcomes of the Swiss intervention are currently being evaluated in a mixed-methods study and have not been published yet. We received personal communication regarding the trial's preliminary results, related conclusions and lessons learned, which we included in the development process of our behavioural intervention. This intervention was guided by the IMB model and included four individual sexual risk counselling sessions accompanied by an e-health assisted intervention. For the current project, we have opted for a completely web-based intervention, as it will improve implementation in routine care when compared to a behavioural intervention that includes face-to-face counselling.

The content of the intervention will consist of interactive questions, text-based modules, and videos addressing information, motivation, and behavioural skills. It will comprise four modules:

- **Module 1**, “Hepatitis C & I” will focus on self-reflection and exploring participants’ intrinsic motivation to reduce the risk of HCV infection using filmed role models. The videos are based on modelling principles of behaviour where peers tell real stories about their experiences and challenges with HCV related risk behaviours and how they addressed these challenges. After watching the video(s), participants will answer self-reflective questions and questions regarding personal motivation to reduce their HCV risk.

- **Module 2**, “What is important to know?” will focus on increasing HCV related knowledge. Participants will receive tailored information about modes of transmission and a summary of personal HCV risk factors based on the participant’s earlier disclosed risk behaviour in the study questionnaire (i.e. the items of the HCV-MOSAIC risk score and other HCV related risk factors).

- **Module 3**, “Making my plan”, will identify the necessary steps to achieve behavioural goals, leading to a personalized risk reduction plan.

1. The user will be able to choose tailored personal goals from a set of options based on the participant’s answers to the study questionnaire. They will also be offered the option to formulate their own goal(s) using an open text field.

2. Relevant solutions for personal psychosocial/cognitive barriers to reducing HCV-related sexual risk behaviour will then be offered according to the chosen goals. To promote skills efficacy for practicing risk reduction strategies modules will address on a tailored basis communication between sex partners, such as suggested conversation openers and discussion scenarios. It will also include decision-making tips during social-sexual interaction within the high-risk network. Videos will demonstrate risk reduction techniques specific to high-risk settings (such as group sex) and will link users to available HCV-related risk reduction tools.

3. The participant will finalize a personal risk reduction plan.

- **Module 4**, “Evaluating my plan”, will focus on the evaluation of the risk reduction plan. After one or two months, depending on the preference of the participant, the participant will receive an email notification to return to the intervention to evaluate the goals. In this final module, the participant will be able to reflect on the risk reduction plan and adjust the goals if desired. Participants will be encouraged to formulate a new action plan and return

for evaluation in case goals have not been achieved. If the participant would need extra support through personal counselling, webcam or telephone counselling will be offered.

Tailoring

The intervention will be offered in a tailored fashion, meaning that it will be adapted based on the study questionnaire and personal needs of each user. Men will receive information related to their situation, making the intervention more concise and relevant, which has shown to result in increased adherence to the intervention.⁵⁵ Nevertheless, some information will generally be relevant and thus provided to all MSM. The persuasive design model⁵⁶ will be used to select and implement persuasive features (e.g. praise, suggestion) in the intervention.

The intervention will be offered during the intervention period of 18 months on a website that will be dedicated to the intervention and will be able to be used on a computer or mobile phone. Participants can log out and return to the behavioural intervention at any time using their personal login code. Men who do not complete all the modules of the intervention as intended, will receive an email reminder or text message that reminds them to visit the website.

5.2 Arm II: home-based testing intervention

The second arm will consist of an additional patient-initiated home-based HCV testing service. The service will offer 4 free-of-charge HCV RNA tests, which can be obtained online. It involves home-based HCV testing using self-sampled dried blood spots (DBS) (i.e., home-collection testing involving a certified laboratory) that has already been developed and is in use for purchase on the NoMoreC website (<https://nomorec.nl/thuis-testen-op-hepc>). This internet-mediated home-based HCV testing service is currently ongoing and evaluated by us as part of the MC free initiative (www.mcfree.nl), a collaboration of relevant stakeholders that aims to reduce the incidence of HCV infections among MSM in Amsterdam. This service allows men at high risk for HCV infection to take control and test for the presence of HCV-RNA. The self-sampling DBS has been previously validated and shown to be effective (see **Chapter 6**).

After randomization at month 6, a 100% discount code will be provided on the (ICECREAM) study website, which can be used on the NoMoreC website. In order to obtain the test kits, the participants will have to create an account on the NoMoreC website. The test kits will be delivered to the address provided by the participant in a blank envelop, along with paper instructions and package materials for returning the test kits

with the self-collected DBS sample. If the participant prefers not to have the test kits delivered to a home address, the option will be offered to obtain the test kits from the project leader at the Public Health Service of Amsterdam. After obtaining the DBS, the DBS kit can be returned by mail to the laboratory of the Amsterdam UMC, location AMC for HCV RNA testing. Test results will be uploaded and can be obtained by the participant online via the NoMoreC website using their personal account. In case of a HCV RNA positive test result, participants will be offered linkage to clinical care as soon as possible and start HCV treatment if indicated. A referral letter with the test result and information on the type of the test that was done can be downloaded and printed or sent to an email address to assist MSM to discuss their test results with their physician. Partner referral will be provided as part of routine procedures. In addition, the project leader will contact participants by telephone to ensure that they are referred to adequate medical care.

The HCV RNA testing service can be used for 18 months. We will recommend men to use the free-of-charge HCV tests in between visits at their HIV treatment center or STI/PrEP/sexual health center, in particular when they perceive themselves at HCV reinfection risk, assuming testing behaviour is driven by suspected HCV exposure. A reminder to use the tests will be added to the email invitations of the study questionnaire at month 12 and 18 (i.e. month 6 and 12 of the intervention period).

5.3 Arm III: behavioural and home-based testing intervention combined

The third arm combines the behavioural intervention with the testing intervention. In this arm, both interventions will be offered to participants for 18 months. We hypothesize that the combined intervention will lead to the greatest reduction in risk behaviour. Additional testing can have different effects on risk behaviour, as described in [Chapter 1.4](#). However, there is no data available on the effect of additional HCV testing among men who have sex with men that can support our hypothesis. Nevertheless, we believe that the testing intervention in combination with the behavioural intervention can increase awareness around HCV and possibly reduce risk behaviour the most.

6. NON-INVESTIGATIONAL PRODUCT

6.1 Name and description of the self-sampled dried blot spots

The home-based HCV-RNA testing service involves self-sampling of blood by finger prick on a paper card at home (a dried blood spot, DBS). The participant will be given the home kits with paper instructions, including a link to an instructional video, on how to safely self-sample 5 drops of blood on filter paper (Whatman 903). The participant will send the DBS sample to the laboratory of the Amsterdam UMC, location AMC, according to instructions.

The home kit includes the following items:

- Paper instructions
- Alcohol swap
- 2 lancets – Type: BD Microtainer® contact-activated lancet
- Whatman 903 filter paper card with 5 preprinted circles
- Sterile gauze
- Bandaid
- Sealable plastic bag with desiccant
- Return envelope (postage paid)

When an ssDBS arrives at the lab, the arrival date will be marked on the card. Viral RNA will be measured within 3 – 7 days after arrival at the laboratory.

6.2 Summary of findings from clinical studies

A systematic literature review by Greenman et al. of DBS for HCV RNA detection supports the potential use of DBS for HCV RNA detection.⁵⁷ DBS is expected to adequately detect and quantify HCV RNA for the purpose of diagnosing HCV infection. The reviewed DBS studies reported varying viral load detection limits, between 2.2 – 3.4 log IU/ml; 0.5-1.7 log IU/ml higher compared to plasma sample tests.⁵⁸⁻⁶¹

In addition, DBS self-sampling has been found to be a feasible technique for the detection of HCV RNA and is currently being used by the Dutch team (Prinsen et al, work in progress; <https://nomorec.nl/en/testing-at-home-for-hepc>). They initially validated the use of DBS to measure HCV RNA loads using whole blood samples spotted on Whatman 903 filter paper by a laboratory technician. The HCV RNA loads detected were 1.0-1.6 log IU/ml lower with DBS compared to plasma loads. Although the DBS has higher viral load detection limits than plasma tests, it is suitable for diagnosing patients with active replication, as most patients have viral loads >3.0 log IU/ml.⁵⁹ Therefore, it is anticipated that with the use of DBS method, at least 95% of the HCV positive patients will be diagnosed.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

1. From run-in and post-randomization questionnaires, we will evaluate the proportion at risk of HCV infection (as determined by a HCV-MOSAIC score ≥ 2.0) during the run-in versus intervention periods. The HCV-MOSAIC risk score has been previously validated for acute HCV-infection and is calculated by summing up the beta-coefficients specific to six self-reported risk factors when present in the past 6 months: (i) receptive condomless anal sex (beta 1.1), (ii) sharing sex toys (beta 1.2), (iii) unprotected fisting (beta 0.9), (iv) injecting drug use (beta 1.4), (v) sharing snoring equipment during nasally-administered drug use (beta 1.0), and (vi) ulcerative sexually transmitted infection (beta 1.4). A reduction in the proportion of individuals at risk would demonstrate a positive effect of the intervention on at risk behaviour (as explained in more detail in [Chapter 9.1](#)).

7.1.2 Secondary study parameters/endpoints

1. Incidence rate of HCV reinfection (number of cases of HCV reinfection divided by total person-years of follow-up at risk for reinfection) (self-reported and laboratory data).
2. Incidence rate of any STI (number of cases of chlamydia, gonorrhoea, lymphogranuloma venereum (LGV), genital herpes and/or syphilis divided by total person-years) (self-reported).
3. Changes in HCV-related risk behaviour:
 - a. Changes in the number of sex partners.
 - b. Changes in the number of condomless anal sex acts with casual partners.
 - c. Changes in the individual items of the HCV-MOSAIC risk score:
 - i. Changes in the proportion of individuals reporting receptive condomless anal sex.
 - ii. Changes in the proportion of individuals sharing sex toys.
 - iii. Changes in the proportion of individuals reporting unprotected fisting.
 - iv. Changes in the proportion of individuals reporting injection drug use.

- v. Changes in the proportion of individuals sharing snoring equipment during nasally-administered drug use.
 - vi. Changes in the proportion of individuals reporting ulcerative sexually transmitted infection (syphilis, genital herpes or lymphogranuloma venereum infection).
- d. Proportion of individuals with change in any of the items of the HCV-MOSAIC risk score.
- e. Changes in the frequency of recreational drug use before and during sex.
- f. Changes in the frequency of individuals engaging in group sex activities, including changes in number of events and maximum number of sex partners during an event.
- g. Changes in the proportion of individuals sharing lubricants.
- h. Changes in the proportion of individuals sharing anal douches.
- 4. Changes in the proportion of individuals disinfecting sex toys, skin and/or sex location.
- 5. Changes in the sexual wellbeing score.

7.1.3 Other study parameters

1. Characteristics of the study population:
 - a. Age
 - b. Ethnicity
 - c. Gender identity
 - d. Educational level
 - e. HIV-status
 - f. PrEP use
 - g. HCV history (number of infection(s), type of treatment, year of infection(s), impact of treatment(s))
2. Intervention-related endpoints: behavioural intervention
 - a. The proportion of individuals reporting change in the risk behaviour identified in the goal setting module of the behavioural intervention.
 - b. Website statistics: e.g., frequency of use, time spent on the intervention and the proportion of individuals completing all modules of the intervention.
 - c. Type of goals set in the behavioural intervention.
 - d. Usability and acceptability of the behavioural intervention.
3. Intervention-related endpoints: testing intervention

- a. The proportion of free HCV tests used (the total number of free HCV tests used divided by the total number of distributed tests).
 - b. The proportion of HCV positive test results (the total number of HCV positive test results divided by the total number of free tests used).
 - c. Usability and acceptability of the testing intervention.
4. The number of (home-based) tests obtained and used from other sources.

7.2 Randomisation, blinding and treatment allocation

Centralized randomization will use computer-generated lists of random permuted blocks of six to randomly assign participants to one of the three study arms (1:1:1 randomization). Randomization will take place using a web-based interface, which will immediately inform participants and investigators of the assigned arm. The study will be an unblinded randomized trial, meaning that both participants and researchers will be unblinded to study arms. Intervention allocations cannot be predetermined prior to and during enrolment.

7.3 Study procedures

Questionnaires

After the eligibility check and obtaining informed consent, participants will receive a login code and a link to the study website by email. All questionnaires will be offered online using email notifications or text notifications. After enrolment, participants will be invited to fill out the baseline questionnaire (i.e., at month 0). Subsequently, a questionnaire will be offered to all participants every 6 months (i.e., at month 6, 12, 18 and 24), measuring risk behaviour over the past 6 months. Email reminders will be sent to the participants in case the questionnaire was not completed 1.5 week and 3 weeks after the first email notification was sent.

Run-in period

All participants will receive standard care during the run-in period of six months. HIV-positive MSM will receive standard care during biannual visits at their HIV treatment center, where routine blood testing, including liver enzymes, takes place every 6 months according to national guidelines.⁶² Testing policies for HCV reinfection might differ per HIV treatment center; some centers might perform annual testing and others might only test for HCV RNA in the presence of elevated liver enzymes. In addition, the majority of HIV-positive MSM regularly visits the STI outpatient clinic of a Public Health Service for STI testing.

Standard care among HIV-negative MSM differs. HIV-negative MSM using PrEP will usually receive STI testing at an STI/PrEP/sexual health center. MSM participating in the PrEP projects will routinely visit the STI clinic of the Public Health Service of Amsterdam for PrEP monitoring including STI screening (syphilis, hepatitis B, hepatitis C, HIV, chlamydia and gonorrhoea). MSM enrolled in the PrEP projects at the Public Health Service of Amsterdam are currently being tested for HCV reinfection every 3 to 6 months. HIV-negative MSM not using PrEP are not routinely tested for HCV infection, unless they are notified by a HCV positive sex partner.

Intervention period

After randomization at month 6, participants will be referred to one of the three arms on the study website: (1) the behavioural intervention (see [Chapter 5.1](#)), (2) the testing intervention (see [Chapter 5.2](#)), or (3) the combined intervention (see [Chapter 5.3](#)). In addition to standard care as described above, participants will be offered the intervention(s) for 18 months (month 6-24).

After the end of the study

Additional HCV RNA blood testing will retrospectively be performed to test for HCV reinfection if: 1) the participant did not receive HCV RNA testing in the 6 months prior to the end of the study period, 2) there is a blood sample available for HCV RNA testing at the laboratory of the participating site and 3) the participant provided consent for retrospective HCV RNA testing in the informed consent form. These blood samples are collected during routine visits at the HIV treatment center or during visits at the STI/PreP/sexual health center. All study procedures are shown in [Table 1](#).

| Study procedures | Inclusion | Month 0 | Month 6 | Month 12 | Month 18 | Month 24 | After the end of the study |
|--------------------------|-----------|---------|---------|----------|----------|----------|----------------------------|
| Eligibility check | x | | | | | | |
| Informed consent | x | | | | | | |
| Questionnaire | | x | x | x | x | x | |
| Online randomization | | | x | | | | |
| Behavioural intervention | | | x | x | x | | |
| Testing intervention | | | x | x | x | | |
| Combined intervention | | | x | x | x | | |
| HCV RNA testing in a | | | | | | | x |

| | | | | | | | |
|----------------------|--|--|--|--|--|--|--|
| stored blood sample* | | | | | | | |
|----------------------|--|--|--|--|--|--|--|

* in case no HCV RNA test was performed in the last 6 months of the study period.

Table 1: Study procedures ICECREAM study

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Individual subjects that chose to withdraw from the study will be replaced by other participants if recruitment is still ongoing.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 Data Safety Monitoring Board (DSMB) / Safety Committee

We determine that the associated risk and benefits are negligible for the participants included in this study. A data safety monitoring board was therefore deemed unnecessary.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

The primary outcome is the proportion at risk of HCV infection (as determined by a HCV-MOSAIC score ≥ 2.0) during the run-in versus intervention periods. The score is calculated by summing up the beta-coefficients specific to six self-reported risk factors when present in the previous 6 months (see [Chapter 7.1.1](#)). The HCV-MOSAIC risk score has been previously validated for acute (primary) HCV-infection in HIV-positive MSM and the optimal cut-off to predict HCV positivity was defined at ≥ 2.0 .⁶³ In addition, we recently evaluated whether the risk score could also identify individuals at high-risk of HCV reinfection, showing comparable performance (The Area Under the ROC Curve = 0.76) to that of primary acute HCV-infection.⁶⁴

The six items of the HCV-MOSAIC risk score will be obtained using the answers from the study questionnaire every six months. The proportion achieving the primary outcome will be summarized at month 6, 12, 18 and 24 visits within each study arm. The probability of the primary outcome will be compared between the run-in (month 6) and intervention periods (month 12, month 18, month 24) using a mixed-effect logistic regression model. In this model, each individual will serve as their own control and between-individual differences at baseline will be accounted for using a random-intercept. Pre versus post-intervention odds ratios (ORs) and their 95% confidence intervals (CI) will be estimated and stratified on study arm, allowing us to identify interventions with significant differences. No multivariable adjustments will be applied. Additional analysis will be conducted in which ORs between arms will be compared by including and testing an interaction term between period and arm in the model (two arms at a time, for a possible three comparisons). No *p*-value adjustments will be made for multiple comparisons to avoid unnecessary correction on the possibly underpowered test for interaction.⁶⁵

Analyses will be performed by intention to treat (ITT) and per protocol (PP). Both analyses will only include individuals completing the lead-in phase (month-6). ITT analysis is defined by including all observations, while assuming that any individual lost to follow-up did not achieve the primary endpoint. PP analysis is defined by including all available observations, while excluding observations after an individual has been lost to follow-up. Subgroup analysis will also be conducted in order to determine whether individuals with certain characteristics are more likely to have a decrease in HCV-MOSAIC score.

9.2 Secondary study parameter(s)

Incidence rates of HCV reinfections and STIs will be calculated at the end of follow-up. Incidence of HCV reinfection will be examined during the lead-in and intervention periods of the RT. Considering few HCV reinfections are likely to occur, we intend to analyse differences in periods, along with associated risk-factors, using Bayesian exponential survival regression models with non to weakly informative *a priori* distributions.⁶⁶

For all other secondary study parameters, continuous variables will be summarized using means or medians and categorical variables using counts and percentages at each study visit. Changes over time will be described for HCV related risk behaviour, disinfection behaviour and sexual wellbeing. We will use statistical regression methods specific to the endpoint (logistic for binary outcomes, linear for continuous variables), corrected for repeated measurements within individuals (using mixed-effect methods) to investigate changes between lead-in and intervention periods and associated determinants. Outcomes will also be compared across the 3 arms.

9.3 Other study parameters

Descriptive statistical analyses will be performed to describe study population characteristics, intervention-related outcomes (e.g. use of the services, acceptability and usability) and the number of (home-based) tests obtained and used from other sources.

9.4 Interim analysis

No study arms plan to be discontinued due to preliminary signals of inefficaciousness. No harmful effects are remotely expected during participation in the arms. Therefore, no interim analysis is planned.

9.5 Mathematical modelling

Using mathematical modelling and incorporating the outcomes of the RT, we will evaluate the impact of the RT interventions on reinfection incidence and onward transmission taking the increased uptake of DAA and the undiagnosed population into account. The impact of HCV awareness, early diagnosis and treatment on this HCV spread will be investigated. We will build on previous and ongoing modelling work: a deterministic mathematical model that simulates both HCV and HIV transmission dynamics among MSM simultaneously, which is currently being developed, and an individual based model for HCV and HIV transmission dynamics among people who use drugs.¹¹ Parameters will be derived from the ICECREAM study and from literature. Mathematical modelling will be performed in collaboration with the Infectious Disease Dynamics Group at the University Medical Center Utrecht.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Seventh revision, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) of Dutch law.

10.2 Recruitment and consent

We will invite MSM aged 18 years or older with a history of a cured or spontaneously cleared HCV infection and in care at an HIV treatment center or using STI/PrEP related care to participate in the RT. Treating physicians and nurses at the study centers will propose the study to individuals meeting the inclusion criteria. Treating physicians include infectious disease specialists and doctors from the STI outpatient clinic and PrEP projects. Nurses include HIV nurse consultants/specialists and nurses from the STI outpatient clinic and PrEP projects. The HCV infection in the past will be confirmed by the treating physicians or nurses who enrol the participant by checking the laboratory results in the patient files. Information will be given both verbally and in a written information brochure. Adequate opportunity will be provided to the potential subject to ask questions. After written informed consent is obtained, the subjects will be included in the study. A copy of the signed informed consent form will be given to the participant. The informed consent forms will be retained at the participating site. A copy of the informed consent form will be sent to the Public Health Service of Amsterdam (coordinating center).

10.3 Benefits and risks assessment, group relatedness

In this study, only adults will be included. The questionnaires and interventions that will be offered in this study will not pose any other or additional risk than standard care.

Participants will be exposed to five questionnaires, containing personal questions about sexual risk behaviour and drug use. Both the questionnaires and the interventions can make the participants more aware of their HCV risk, which could make participants feel at unease. However, we think that MSM who do not want to be confronted with their HCV risk behaviour and risk will not be interested in participating in this study.

A benefit of participating in the study might be a decreased risk of HCV infection and lower levels of risk behaviour, depending on the outcome of the study. Furthermore, the participants assigned to the testing or combined intervention will receive 4 free of charge home-based tests, which might lead to more frequent, patient-initiated, testing and

possibly earlier diagnosis of HCV infection and start of treatment. Another possible benefit could be that men can contribute to reducing the spread of HCV in the MSM community.

We classify this study as having a low chance of possible risk and a low degree of harm, leading to a negligible risk to participants.

10.4 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7 of the WMO. The reviewing committee of the AMC is of the opinion that there are no additional risks for the research subjects participating in this study, they therefore granted dispensation from the WMO subject insurance.

10.5 Incentives

No incentives will be provided to the participants.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

After obtaining informed consent, the treating physician/nurse will send the following details of the participant to the project leader at the Public Health Service of Amsterdam via Secure-email:

- Contact details:
 - First name and surname. Required for the linkage of the attached informed consent form to the participant.
 - Email address. Required for sending login data for the study website, email notifications and email reminders for the questionnaires and the intervention(s).
 - Telephone number. Required to contact the participants in case of HCV RNA positive test results.
 - Date of birth. Required to link reinfection data from the STI outpatient clinic to the participant.
- A copy of the informed consent form. The informed consent form contains the subjects consent regarding linkage of data. The signed forms will be retained at the participating site. However, as the linkage will be coordinated by the Public Health Service of Amsterdam, a copy of the informed consent form will be required at the coordinating site.

It will be communicated both verbally and written (in the information brochure and the informed consent form) that the personal data mentioned above, will be transferred from the treating physician/nurse to the project leader at the Public Health Service of Amsterdam via Secure email.

The project leader registers the participant in het personal SQL database (database 1) and generates a random study number for each participant. The study number is communicated to the treating physician/nurse in the inclusion center by a reply email to the Secure-email mentioned above.

Data will be collected as follows:

- Self-reported clinical and behavioural data of participants will be collected by online questionnaires using LimeSurvey software.
- Data on the use of the services of the behavioural intervention will be collected from the study website, including the exposure to and intensity of use of each of

the components of the online behavioural intervention (using log-data) if assigned to intervention I or III.

- Data on the number of free HCV home-based test(s) used and their test results will be collected from the Content Management System (CMS) from the NoMoreC website if assigned to intervention II or III.
- Data on HCV reinfection (HCV RNA test date(s), test results and HCV treatment) will be collected from laboratory and clinical files of the participating sites, and the Dutch HIV monitoring foundation (in Dutch: Stichting HIV Monitoring, SHM):
 - HIV treatment center: only for HIV-positive participants. Linkage will be performed using study number if the participant provided consent via the informed consent form. Linkage to SHM data will be through the HIV treatment centers using routine procedures.
 - STI/PrEP/sexual health center: for HIV-negative participants and HIV-positive participants (HIV-positive patients also visit the STI outpatient clinic at the Public Health Center of Amsterdam). Linkage will be performed using name and date of birth to link the STI data.
- Additional HCV RNA blood testing will retrospectively be performed to test for HCV reinfection if: 1) the participant did not receive HCV RNA testing in the 6 months prior to the end of the study period, 2) there is a blood sample available for HCV RNA testing at the laboratory of the participating site and 3) the participant provided consent for retrospective HCV RNA testing in the informed consent form. These blood samples are routinely collected during visits at the HIV treatment center or at the STI/PrEP/sexual health center every 3-6 months (see [Chapter 7.3](#)) and are retained at the laboratory for a minimum of 2 years according to law.

The data manager at the Public Health Service of Amsterdam will import the data from the questionnaires, the behavioural intervention, the NoMoreC website, HCV test results and clinical data into the Research SQL database (database 2).

The data of the participants will be stored in two separate databases: 1) containing study number and directly identifiable personal data (subject identification code list) and 2) containing study number and study data (e.g., sexual risk behaviour data). The subject identification code list will be safeguarded by a key and will only be accessible by the project leader and data manager if necessary. A subject identification code list (database 1) will be used to link the data to the subject. This code list will be kept until 5 years after

the end of the project. The DBS samples will be kept until 1 year after the end of the project. All other study data (database 2) will be stored for 15 years.

11.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial and amendments. We will not be able to trace serious adverse events/ serious adverse reactions as only one site visit is required at the start of the study and all further study procedures will take place online or at home. No harmful effects are remotely expected during participation.

11.4 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as completion of the final questionnaire by the last included subject. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.5 Public disclosure and publication policy

We intent to publish study outcomes in the most appropriate peer-reviewed scientific journals and at scientific conferences. Authorship will follow the guidelines defined by the international Committee of Medical Journal Editors. In addition, participants, their community and relevant stakeholder will be informed in layman's terms about (the outcomes of) the study.

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